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Background: The risk of bilateral breast cancer is substantially higher than the risk of unilateral disease and associated with early age at onset of the initial breast cancer. Of the many established risk factors for breast cancer, only family history has been consistently shown to be associated with bilateral disease.
Methods: We analyzed a population-based cohort of 123,757 women with a first primary breast cancer diagnosed in Sweden from 1970 to 2000 and identified 6,550 women with a bilateral breast cancer.
Results: Incidence of synchronous bilateral breast cancer mimics that of unilateral breast cancer. During 20 years from initial diagnosis, the incidence of metachronous cancer decreased from about 800 to 400 per 10^5 person-years in patients first diagnosed before age 45, whilst the incidence remained stable at 500 to 600 per 10^5 among those who were older at diagnosis of first cancer.
Conclusions: The finding of breast cancer being simultaneously diagnosed in two breasts has an incidence far beyond the expected, but is probably not explained by genetic background rather environmental factors. The incidence pattern of metachronous bilateral cancer by age and follow-up time fits neither a model of highly penetrant genes, nor a model assuming only aggregation of environmental risk factors.

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1. Introduction

One million women are diagnosed with breast cancer each year globally. Between 8 and 12 percent of women in the western world will be diagnosed with the disease during their lifetime and the incidence is increasing (1). In Sweden, the increase of the disease is likely to be partly attributable to the introduction of mammography screening in the 1980´s and the widespread use of postmenopausal hormone replacement therapy (HRT) (2). The epidemiological evidence seems to indicate that a high proportion of breast cancers arise in a susceptible minority of women (3). The risk of contralateral breast cancer (CBC) is probably even more genetically determined and to a lesser extent influenced by mammography screening and HRT but to some degree dependant on given adjuvant therapy.

The incidence of CBC has been shown to have a constant annual rate of approximately 0.5% (4). This is in contrast to the rate of breast cancer in the general population, which is strongly age dependent. In addition, breast cancer incidence in first degree relatives suggest that the relative's risk rises until the age when the proband was diagnosed with breast cancer and remains constant thereafter (3). These observations would suggest that the age of onset for the disease is genetically determined. The estimations are, however, based on a small data set with limited follow up. Few studies have estimated the risk pattern of CBC, the risk pattern in relatives, including twins, in a large population based material with a sufficiently long follow up.

2. Body

Research accomplishments as outlined in the Statement of Work.
Task 1. Database management of Swedish Breast Cancer Cohort data file, Months 1-5:

a. Firstly we planned linkage of the Swedish Cancer Register to the Causes of Death Register and the immigration and emigration register by a unique personal identification number.
b. Secondly we planned to institute a database quality control program to check for errors and inconsistencies in the merged file from the Swedish Cancer Register, causes of death register and the immi-/emigration register.
c. Thirdly we planned to perform structural work of organizing the cohort on an individual level with an identifying variable for each breast cancer in succession.
d. Finally we planned to perform additional statistical programming in order to create and translate new variables to allow for entry, exit and censoring in the study.

Summary:
We have successfully established a database of all breast cancer cases in Sweden 1958-2000 with information on censor data. An extensive effort has been made to clean the data set of errors and we are now confident that it can be used for analysis. Database used for calculation of results in Appendix I.

Task 2. Creating a population file of the Swedish file population from 1958-2000. Months 6-7:

a. The initial step after receiving the file from Statistics Sweden was to calculate a mean population in 5 year age and calendar period categories.
b. Using breast cancer counts in Sweden from the constructed Breast Cancer Cohort file 1958-2000 we planned to generate background population based breast cancer incidence rates to be used for Standardized incidence ratio calculations.

Summary:
A population count file has been establish using information from Statistics Sweden for 1958-2000 in order to calculate unilateral breast cancer rates that in turn has been used for Standardized incidence ratios. See Appendix I, Table 2.

Task 3. Data analysis of the Breast Cancer Cohort. Months 8-9:

a. We anticipated and planned for a detailed data analysis once the final data set would be constructed.

Summary:

The data analysis of the breast cancer cohort including calculation of incidence rates of contralateral breast cancer and furthermore modeling the risk of contralateral breast cancer in relation to the risk of unilateral breast cancer was done. This work was cumbersome and required extensive works by the research group especially our biostatisticians. See Appendix I, Figure 1,2,3 and Table 2,3,4

Task 4. Database management of the Twin and Multi-Generation Register files. Months 10-12:

a. We planned linkage of the most updated population based cancer and death files to the Nordic twin registers and the Swedish Multi-Generation Register using the unique personal identification number.
b. Since the merged files had multiple countries of origin and thus had differing structures and furthermore some of the files were of a very large magnitude we planned to institute a quality control program to minimize errors and inconsistencies.
c. A final file was to be output into a SAS data set.

Summary:

Twin cohorts: We started by merging country specific data set from Sweden, Finland and Denmark containing information on female twin pairs of which at least one sister had a diagnosis of breast cancer. The individual files were checked for inconsistencies and variables were harmonized to allow for merging the 3 sets into one Nordic twin breast cancer file containing information on breast cancer diagnosis and censoring information. A total of 2140 twin-pairs with breast cancer were identified.

The Multi-Generation Cancer Database: Statistics Sweden maintains a "Multi-Generation Register" where children, offspring, born in Sweden in 1932 and later are registered with their parents (those pleading parenthood at birth) as families. The data on families and cancers have a complete coverage, baring some groups of deceased offspring, which affect those born in the 1930s and who died before 1991. This Register was linked by the individually unique national registration number to the Cancer Registry from years 1958-2000. However, because of some inaccuracies in vital status determination in the first years of cancer registration, parental cancer in the present study was diagnosed between years 1961 and 2000. Cancer registration is considered to be close to 100% currently. A 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) and subsequent ICD classifications are available. Additional linkage was carried out to the national census data to obtain socio-economic background data and to death notifications for vital status determination. The linkages were carried out at Statistics Sweden who delivered the final matched records in an unidentified form.

After considerable data management and quality assurance by IT division within our department the 'Multi-Generation Cancer Database' in an Oracle environment was created. The Database includes more than 11 million individuals which are structured into 3.1 millions nuclear families. The Database covers years 1961 to 2000 from the Swedish Cancer Registry, and includes 190,132 and 26,391 breast cancers in mothers and daughters, respectively. In the two generations, 2452 affected mother-daughter pairs and 540 sister-sister pairs are recorded.

Task 5. Data analysis of the Twin and Multi-Generation cohort. Months 13-14:

a. The data analysis will be detailed and analysis of the final data set will be conducted.

Summary:

Twin cohort: Incidence rates of breast cancer in the unaffected twin sister were calculated. See Appendix II, Table 1, Table 2. Nelson-Aalen hazard curves were calculated estimating the risk in the unaffected twin sister, stratified by zygosity. Appendix II, Figure 1.

Multi-Generation cohort: Incidence rates of breast cancer in the unaffected female individual in the family was calculated, taking into consideration several options which individual to regard as the index case. See Appendix II, Figures 2-5.

Task 6. Report and Manuscript Production. Months 15-18:
a. Manuscripts were to be prepared.
b. A final report of the findings was to be written.

Summary:
1. Contralateral breast cancer article has been prepared and has been submitted for publication. See Appendix I.

2. Occurrence patterns of Inherited Breast Cancer. A Scandinavian Twin and Sibling Study. This article is addressing the risk of breast cancer in twins and in sisters and mothers. It is manuscript in progress, we are currently doing the final analysis of the sisters and mothers with breast cancer to added to the article. It will be submitted shortly. We present only figures and tables for the report. See Appendix II.

3. Key research accomplishments

1. The incidence pattern of metachronous bilateral cancer by age and follow-up time fits neither a model of highly penetrant genes, nor a model assuming only aggregation of environmental risk factors.
2. The incidence of synchronous bilateral cancer increased whilst the incidence of metachronous cancer decreased markedly over the period 1970-2000.
3. We found an age–independent risk by 1st twins age of onset of breast cancer, with 2 different risk levels for monozygotic and dizygotic twins.

4. Reportable outcomes

1. Changing patterns of bilateral breast cancer, manuscript submitted to Journal of National Cancer Institute. Appendix I.
2. Occurrence patterns of Inherited Breast Cancer. A Scandinavian Twin and Sibling Study. Appendix II. Manuscript to be submitted shortly.
3. Abstract, presented at Medical and Statistical Conference in Leiden, Aug. 2004 by Prof. Marie Reilly, co-applicant.
4. Presentation at Karolinska Institute, Mini symposium, Fall 2004 by Prof. Marie Reilly, co-applicant.

5. Conclusions

1. A woman's contralateral breast is at a high risk of developing breast cancer through the entire life span of the woman, putting her at a lifelong risk.
2. It seems that the treatment of the initial breast cancer is having a strong impact in decreasing the risk of bilateral breast cancer.
3. A model to determine the underlying cause of bilateral breast cancer would have to adjust for strong genetic factors as well as an accumulation of environmental exposures.

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7. Appendices

Appendix I – "Changing patterns of bilateral breast cancer", manuscript
Appendix II - Tables and figures for manuscript in progress: "Occurrence patterns of Inherited Breast Cancer". A Scandinavian Twin and Sibling Study.

Changing Patterns of Bilateral breast cancer

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ABSTRACT

Background: Women with breast cancer are at high risk of developing contralateral breast cancer. Little is known, however, about the relation between synchronous versus metachronous bilateral breast cancer or occurrence patterns of bilateral breast cancer in relation to age, duration of follow-up, and calendar time.

Methods: We analyzed a population-based cohort of 123,757 women with a first primary breast cancer diagnosed in Sweden from 1970 to 2000 and identified 6550 women with a bilateral breast cancer. Complete ascertainment of bilateral breast cancers and deaths was achieved by means of record linkage.

Results: The incidence of synchronous breast cancer (diagnosed within three months after a first breast cancer) doubled during the 1970s, whilst the incidence of metachronous cancer decreased by about 50% (p for trend < 0.001) since the early 1980s. During 20 years from initial diagnosis, the incidence of metachronous cancer decreased from about 800 to 400 per 10^5 person-years in patients first diagnosed before age 45, whilst the incidence remained stable at 500 to 600 per 10^5 among those who were older at diagnosis of first cancer. After 30 years of follow-up, the cumulative risk of metachronous bilateral breast cancer approached 15% regardless of age at first primary breast cancer.

Conclusions: The incidence pattern of metachronous bilateral cancer by age and follow-up time fits neither a model of highly penetrant genes, nor a model assuming only aggregation of environmental risk factors. Over calendar time, the incidence of synchronous bilateral cancer increased whilst the incidence of metachronous cancer decreased markedly.

INTRODUCTION

An estimated 73 000 women in Sweden have a history of breast cancer [1]. The corresponding figure in the US is close to 2.2 million women given a higher incidence and larger population [2]. Hence, any progress in understanding the biology of bilateral breast cancer, which has been estimated to be a proportion of 2-11% of all breast cancer cases [3], and identifying women at high risk of a bilateral breast cancer, might have far reaching consequences.

With retinoblastoma of the eye as a model, detailed studies of cancer incidence in a paired organ paved the way for one of the most important discoveries in modern cancer biology, namely the existence of tumor suppressor genes [4, 5]. Early onset [6] and multiple lesions became established characteristics for a strong genetic component in cancers such as large bowel cancer in subjects with familial adenomatos polyposis [7]. Similar to bilateral retinoblastoma and familial adenomatos polyposis, bilateral breast cancer also represents multi-focal malignant transformation in one and the same tissue. However, unlike retinoblastoma that typically arises in young children, breast cancer occurs at ages when both breasts have been affected by the same genetic and environmental factors during several decades. However, if multi-focal breast cancer is predominantly determined by germ line mutations that affect all somatic cells equally, then we might expect early onset and probably age clustering of bilateral disease.

The risk of bilateral breast cancer is substantially higher than the risk of unilateral disease [8, 3]. The risk of bilateral breast cancer is associated with early age at onset of the initial breast cancer [9, 10, 11]. Of the many established risk factors for breast cancer, only family history has been consistently shown to be associated with bilateral disease [9, 12, 11]. Futhermore, only 5 percent of all bilateral breast cancer cases are mutation carriers for the high penetrance genes BRCA1 and 2 [13]. Radiotherapy following breast cancer has been shown to increase the

risk of bilateral breast cancer 10 years following the primary tumor [14]. A reduction of bilateral breast cancer incidence by 30-50% has been seen after adjuvant systemic therapy [15-19], further complicating the interpretation of inheritance patterns.

Low statistical power, uncertain assessment of bilateral primary cancers, limited age ranges, and short follow-up [3] have hampered studies of occurrence patterns of bilateral breast cancer. Here we take advantage of a large, nationwide cohort in Sweden to analyze bilateral breast cancers by age of onset over a 30-year period. The study also allows us to assess temporal trends that might have occurred as a consequence of changes in clinical management, notably routine mammographic examination, and widespread use of systemic adjuvant treatment.

PATIENTS AND METHODS

Study Cohort

The study cohort was obtained from the nation-wide Swedish Cancer Registry, established in 1958. Reporting to the registry of all newly diagnosed malignant diseases is mandatory both for clinicians and for pathologists. During the period of our study, the register was estimated to be at least 98% complete [20]. For each notified cancer, the register includes the individually unique national registration number, ICD-code and date of diagnosis. Information on stage of disease and treatment is not included in the Swedish Cancer Register. Using the national registration number, the Cancer Register can be linked to the nation-wide Cause of Death Register and information on immigration and emigration from the Total Population Register. This linkage allows complete follow-up with regard to vital status for all individuals notified to the Cancer Registry.

Becuase laterality of breast cancer was not coded prior to 1970, we restricted the study cohort to diagnoses in the period 1970-2000. During this period all 138,372 women with a first primary breast cancer were selected. We excluded 8123 women for whom the history of

breast cancer was uncertain because they had immigrated to Sweden. Another 6492 women were excluded for having a malignant tumor other than in the breast prior to the first breast cancer. After these exclusions, our cohort for final analysis comprised a total of 123,757 women with a first primary invasive breast cancer.

Statistical Methods

Unilateral breast cancer incidence rates were calculated for 5-year age groups and 5-year calendar periods using Swedish population counts. Second primary breast cancers diagnosed within three months of the first primary were categorized as synchronous, the remainder as metachronous. Synchronous bilateral breast cancer was regarded as a simultaneous clinical event, and thus the incidence was calculated as for unilateral breast cancer using the Swedish female population counts.

The incidence rate of metachronous breast cancer was calculated using as the denominator the accumulated person-years at risk among women with unilateral breast cancer. The person-time at risk started at the date of diagnosis of first breast cancer and continued until diagnosis of bilateral breast cancer or a diagnosis of any other malignant disease, emigration, death, or end of follow-up (December 31, 2000), whichever came first.

For metachronous bilateral breast cancer, standardized incidence ratios (SIRs) were calculated as the ratio of the observed number of cases during the follow-up to the expected number of cases. The expected number of bilateral breast cancers was calculated using person years accumulated by the unilateral breast cancer cases, multiplied by the age- and calendar-period-specific unilateral breast cancer incidence rates as reference. Thus, the SIR provides a comparison of the risk of bilateral breast cancer relative to unilateral breast cancer at a given calendar time and age.

We used Poisson regression modeling to examine the independent effects of age, calendar period, and time-since-diagnosis on incidence. We also used Nelson-Aalen estimates for graphical displays of cumulative incidence [21].

All data preparation and analysis was done using the SAS Statistical package, version 8.2 [22].

RESULTS

The cohort of 123,757 women with a first breast cancer diagnosis between 1970 and 2000 generated 879,211 person-years of follow-up and 6,550 cases of bilateral breast cancer of which 1893 were classified as synchronous (Table 1). The number of bilateral breast cancers increased steadily over time. The median time interval between diagnosis of the first and the second primary breast cancer was 4.8 years.

Synchronous Bilateral breast cancer

Overall, about 30% of all bilateral cancers in the cohort were classified as synchronous (Table 1). Due to truncation, the metachronous cancers in the earlier periods are underrepresented. To overcome this source of bias, we calculated the proportion of synchronous to all bilateral cancers diagnosed within the same five-year calendar period and noted an increasing trend over time (Table 1).

Overall, approximately 1.6 synchronous cancers occurred per 10^5 person-years at risk. The age-incidence pattern of synchronous breast cancer seems to mimic the unilateral age pattern, although the absolute rates of synchronous bilateral cancer were two orders of magnitude lower than those of unilateral (Figure 1). This age pattern was also evident using unilateral breast cancers rather than total population as the denominator (data not shown). The incidence of synchronous cancer increased from 1970 until the mid 80's and remained approximately constant thereafter (Figure 2).

Metachronous Bilateral breast cancer

The incidence rate of metachronous breast cancer decreased markedly with increasing age at diagnosis, from $800/10^5$ person-years (0.8 percent per year) below age 50 to approximately $550/10^5$ person-years at age 50 and above (Figure 1). In contrast to the stable incidence rate of synchronous disease from the 1980s, the incidence rate of metachronous cancer decreased by almost one third over the study period from $640/10^5$ in 1970 to $440/10^5$ in 2000 (Figure 2).

In order to investigate the effects of age at and time since first diagnosis we plotted stratified incidence rates (Figure 3). During follow-up, the incidence rate of metachronous cancer decreased gradually among women who were younger than 45 years at diagnosis of the first breast cancer, from approximately $800/10^5$ person-years within the first 10 years to $450/10^5$ after more than 20 years. In contrast, the incidence of metachronous cancer remained fairly stable during follow-up among women who were older than 45 years when their first breast cancer was diagnosed.

To quantify the cumulative risk for metachronous disease over time, we present Nelson-Aalen hazard estimates (Figure 4). The higher hazard (i.e. steeper slope) during the first 10 years after diagnosis for premenopausal women (Age<45) is consistent with the incidence pattern seen in Figure 3. Approximately 7%, or one woman in 14, diagnosed with breast cancer before 45 years will develop a bilateral cancer within 10 years. The corresponding figure for a woman with her first primary breast cancer after the age of 45 years is 5.5%, that is one in 18. After 30 years of follow-up, the cumulative risk approaches 15% regardless of age at first primary breast cancer.

Using SIRs to compare incidence rates for metachronous breast cancer, we observed a significant decreasing overall trend ($p<0.001$) from 3.5 in 1970-74 to 2.0 in 2000 (Table 2). This decreasing trend was more evident during the first 10 years of follow-up. For

metachronous disease the SIR was 9.5 (95% CI =7.9-11.3), in women less than 45 years of age, 4.2 (95% CI = 4.0-4.6), for women aged 45-54 years, and 2.3 (95% CI = 2.2-2.3) for women above 54 years of age (data not shown in tables).

Multivariate Analysis of Metachronous Bilateral breast cancer

A Poisson regression model was used to assess the effects of age and calendar period of first diagnosis (Table 3). In order to eliminate the complexity of truncated follow-up, we analyzed the incidence of metachronous breast cancer in the first five years after initial diagnosis. Compared with women who had a first breast cancer 1995-1999, those diagnosed in 1970-1974 were at a 50 percent higher risk of developing bilateral disease. Moreover, following adjustment for calendar time the risk of metachronous cancer was 110 percent higher in a 40 year old compared to a 75-79 year old woman. The incidence rate ratio showed an overall significant decreasing trend for both calendar period and age at diagnosis ($p<0.001$).

In subsequent analyses, taking into consideration time since first primary breast cancer, we found an interaction between age at first diagnosis and time since first diagnosis. This interaction was accommodated in a second Poisson model (Table 4). The decline of the incidence rate ratio with time since diagnosis was much sharper among women who were less than 45 years old at time of diagnosis of the first cancer than among those who were older than 45 years at that time.

DISCUSSION

Before we summarize and discuss our findings, we wish to highlight the inherited difficulties in interpreting the results. Prior to diagnosis of a first cancer, both breasts are identically influenced by genetic and environmental factors. Hence, synchronous bilateral disease is biologically a manifestation of multi-focal malignant transformation. Following a breast cancer diagnosis, the unaffected breast might be further influenced by therapeutic

interventions, chiefly systemic chemotherapy, or hormonal manipulation and metachronous disease could therefore be seen as the net result of multi-focal disease and of therapeutic influences. Theoretically, adjuvant systemic therapy can affect normal breast parenchyma, pre-malignant lesions and cancers. Finally, diagnostic workup of a first primary cancer may determine whether a pre-clinical bilateral cancer becomes detected early and classified as synchronous disease or diagnosed later as metachronous disease.

Our study shows that synchronous bilateral cancer occurs overall in less than 2% of all women newly diagnosed with breast cancer (Table 1), a level similar to previous studies [23-26]. Furthermore, the age-incidence pattern of synchronous cancer is strikingly similar to that of a first primary (Figure 1). The age-dependant incidence pattern of synchronous cancer seen here has to our knowledge been previously unreported. These findings indicate that simultaneous multi-focal malignant transformation in the breast is a rare event with largely the same induction time as unilateral disease. This observation does not support an important role of highly penetrant germ line mutations in the majority of synchronous bilateral breast cancers because germ line mutations typically entail early onset [6]as has been convincingly demonstrated for women with mutated BRCA-1 and BRCA-2 genes [27].

We also found a gradual increase in the incidence of synchronous disease during the 1970s, and a levelling thereafter. Introduction of routine mammography as part of diagnostic workup in women with a first breast cancer probably generated this pattern. It has been demonstrated that the second primary tumor is more dependant on mammography for detection [28]. In the stratified analysis of the proportion of synchronous cancer to all bilateral breast cancer (Table 1), we found an increasing percentage of synchronous cancers over calendar period. As a corollary, some preclinical bilateral cancers, that would have otherwise surfaced clinically later and then been classified as metachronous, now became detected by mammography and considered as synchronous.

The overall incidence rate of metachronous bilateral cancer in this study is compatible with that reported in other investigations, particularly if differences in sample size, age distribution, and follow-up time are taken into account [3, 10, 29, 30]. Among women who had a first breast cancer, the incidence rate of metachronous bilateral cancer was substantially higher than that of a first primary breast cancer among previously healthy women (Figure 1). Moreover, the occurrence of metachronous cancer followed a pattern by age and calendar time that was markedly different from that of unilateral and synchronous bilateral disease. Specifically, the incidence was higher before 50 years of age (Figure 1). Similar metachronous incidence patterns have been shown in several other studies [29-31].

Starting around 1980, the incidence of metachronous bilateral breast cancer declined by about one third until year 2000 (Figure 2, Table 2), probably as a result of randomized trials demonstrating an important breast cancer survival benefit following adjuvant chemotherapy and treatment with anti-oestrogens [15, 16, 32]. As a result, use of adjuvant systemic therapy became part of routine clinical practice. Both anti-oestrogens [15, 16] and chemotherapy [32] were later shown to reduce the incidence of bilateral disease. A large population based study in the US has recently reported decreasing rates of bilateral breast cancer in the last decades on a similar level to ours [8]. However, in a study from Canada no calendar effect was observed, perhaps due to differences between the US and Canada in the use of adjuvant treatment [30].

The incidence of metachronous bilateral breast cancer was particularly high within ten years after diagnosis of the first breast cancer among women younger than 45 years whilst there is no evidence of a striking early surge among older women (Figure 3, Table 4). Similar results of a decreasing incidence in premenopausal women with increasing follow-up has been shown in a study by Harvey and Briton [33] but the pattern could not be detected in another US study by Bernstein [8]. Our data, however, strongly indicate that, as age advances, no sharp

increase in the incidence of bilateral breast cancer is noted (Figure 3). Nevertheless, bilateral, and implicitly multifocal, breast cancer does not show the sharp decline in excess risk with age seen in hereditary bilateral retinoblastoma [4, 5], FAP [7] or women with BRCA1 or BRCA2 mutations [27]. Thus, the evidence is compatible with the view that bilateral breast cancer, whether synchronous or metachronous, does not have as strong genetic determinants as these hereditary malignancies. The proportion of mutation carriers among bilateral breast cancer patients is difficult to estimate, because earlier studies were biased towards carriers of highly penetrant BRCA lesions. It is currently believed that 5% of all women diagnosed with bilateral breast cancer have some defective genes [13] and that this figure increases when bilateral breast cancer clusters in families [34]. Other breast cancer associated genes, such as p53 germ-line mutations [35] and ataxia-teleangiectasia gene [36] do not seem to influence the risk of bilateral breast cancer.

No good marker is presently available for identifying women who may be at increased risk for bilateral breast cancer [27]. At present, family history of the disease, young age of onset and perhaps also lobular histology predict an increased risk of bilateral breast cancer [8, 29]. It is possible that several low to moderately penetrant alterations in susceptibility genes are needed to substantially increase the risk of bilateral breast cancer. Genes whose transcripts regulate estrogen biosynthesis and metabolism pathways, cell cycle control, apoptosis, and ligand-activated estrogen receptor induced transcription and response may be involved. However, little is known of the relevant genetic changes and their likely interpretation with or without environmental exposures involved. Association studies aiming at identifying polymorphisms that differ between women with uni- and bilateral breast cancer would be a useful approach to identify genetically susceptible subgroups.

The strengths of our study include the large size, population-based prospective design and completeness of follow-up. A disadvantage is the lack of information on treatment which

is likely to explain the change in risk of bilateral breast cancer over calendar time. Underreporting of bilateral breast cancers might also influence our findings. However, since mammographic examination of the remaining breast has been routine clinical practice during follow-up of breast cancer patients since the late 1970s, such underreporting should be minimal and unrelated to calendar period or age at first breast cancer diagnosis.

Our approach to calculate SIR may entail underestimation of the true excess risk, because we used expected rates generated by women with two breasts at risk of developing cancer. If we were to adjust these expected rates to only one breast, our SIR values would essentially double. Hence, the relative risk of developing a metachronous bilateral cancer would be five-fold overall (Table 2) and 19-fold in women below 45 years at diagnosis of their first breast cancer. In accordance to this a theoretical model of a woman with 2 breasts at risk, i.e. a twin sister to a breast cancer affected sibling, Peto et al present an incidence rate of $1310/10^5$ in monozygotic sisters to breast cancer patients [31]. This rate is virtually doubled that of bilateral breast cancer. The unaffected sibling has 2 breasts at risk, which would theoretically translate to a rate of $655/10^5$ in a woman with 1 breast at risk, i.e. approximately the rate of bilateral breast cancer observed here and in several other studies [10, 30].

In conclusion, it seems evident that the contralateral breast is at a very high lifetime risk and that routine use of adjuvant chemotherapy and anti-oestrogen therapy sharply reduces the risk of metachronous bilateral breast cancer in recent years. The incidence patterns of bilateral breast cancer seen in our study, indicate that metachronous bilateral breast cancer, appaers to occur among women who are genetically at higher risk for breast cancer than the average Swedish woman. We find no sign of high penetrant mutations being involved to a large extent. In addition, for synchronous breast cancer the incidence pattern is consistent with multifocal breast cancer occurrence.

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Figure legends

Figure 1. Age-specific incidence rates of unilateral, synchronous and metachronous bilateral breast cancer in Sweden 1970-2000. Incidence rates of unilateral and synchronous caner were calculated using the whole population as "population at risk". Incidence rate of metachronous cancer was calculated using women with unilateral breast cancer as "population at risk".

Figure 2. Temporal trends in incidence rates of unilateral, synchronous and metachronous bilateral breast cancer, in Sweden 1970-2000. Incidence rates of unilateral and synchronous cancer were calculated using the whole population as "population at risk". Incidence rate of metachronous cancer was calculated using women with unilateral breast cancer as "population at risk".

Figure 3. Incidence rate of metachronous bilateral breast cancer in Sweden 1970-2000, by age at first primary breast cancer and duration of follow-up.

Figure 4. Nelson-Aalen estimates of cumulative incidence of metachronous breast cancer by time since first primary breast cancer.

Table 1. Number of unilateral and bilateral breast cancers reported to the Swedish Cancer Register during 1970-2000.

Type of breast cancer	Total no.	Calendar period of diagnosis						
		1970-74	1975-79	1980-84	1985-89	1990-94	1995-99	2000
Unilateral	123 757	16 183	18 257	18 647	20 389	22 278	23 159	4 844
Bilateral	6 550	351	759	1 066	1 190	1 341	1 536	307
Synchronous*	1 893	182	242	334	363	324	380	68
Metachronous*	4 657	169	517	732	827	1 017	1 156	239
Synchronous,%$^{\alpha}$		51.8	52.0	61.1	64.9	60.8	67.1	

*Synchronous breast cancers were defined as being diagnosed within 3 month of primary breast cancer and the remainder were defined as metachronous breast cancers.
$^{\alpha}$Synchronous cancer as a proportion of all bilateral breast cancers diagnosed within the same 5 year calendar period.

Table 2. Observed cases (Obs.), standardized incidence ratios (SIR), 95% confidence intervals (CI) of metachronous bilateral breast cancer in relation to calendar period of diagnosis of bilateral breast cancer and time since diagnosis of primary cancer*

	Time since diagnosis of primary cancer, years											
	Overall			0.25-4			5-9			10-29		
Period	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI
1970-74	158	3.5	3.0-4.1	158	3.5	3.0-4.1	-	-	-	-	-	-
1975-79	490	3.4	3.1-3.8	367	3.5	3.1-3.8	123	3.3	2.8-3.9	-	-	-
1980-84	656	3.0	2.7-3.2	357	3.0	2.7-3.4	234	3.0	2.6-3.4	65	2.4	1.9-3.1
1985-89	752	2.5	2.3-2.7	350	2.8	2.5-3.1	226	2.4	2.1-2.7	176	2.2	1.8-2.5
1990-94	919	2.3	2.2-2.5	391	2.5	2.3-2.8	251	2.4	2.1-2.7	277	2.1	1.8-2.3
1995-99	1032	2.3	2.1-2.4	368	2.3	2.1-2.5	285	2.2	2.0-2.5	379	2.2	2.0-2.5
2000+	219	2.0	1.8-2.3	78	2.1	1.7-2.6	62	2.1	1.6-2.7	79	1.9	1.5-2.3
Trend			p<0.001			p<0.001			p=0.005			p=0.12
Overall	4226	2.5	2.4-2.6	2069	2.8	2.7-2.9	1181	2.5	2.4-2.7	976	2.2	2.0-2.3

*Age at diagnosis 40-80 years, calendar period 1970-

Table 3. Incidence rate ratios (IRR) and 95% confidence intervals (CI) from a Poisson model of risk of metachronous bilateral breast cancer using the predictors: calendar period of diagnosis and age at diagnosis of first breast cancer. All cases 1970-1999 included, age 40-79 years and time since diagnosis <5 years.

Category	IRR	95% CI
Calendar period of diagnosis		
1970-74	1.5	(1.2-1.7)
1975-79	1.5	(1.3-1.7)
1980-84	1.3	(1.1-1.6)
1985-89	1.2	(1.0-1.4)
1990-94	1.1	(1.0-1.3)
1995-99	1.0	ref.
Trend	p<0.001	
Age at diagnosis, years		
40-44	2.1	(1.6-2.7)
45-49	1.9	(1.5-2.3)
50-54	1.3	(1.1-1.7)
55-59	1.4	(1.1-1.7)
60-64	1.3	(1.0-1.6)
65-69	1.4	(1.1-1.7)
70-74	1.4	(1.2-1.8)
75-79	1.2	(0.9-1.5)
80	1.0	ref.
Trend	p<0.001	

*All cases diagnosed 1970-1999 included, age 40-80 years and time since diagnosis <5 years.

Table 4. Incidence rate ratios (IRR) and 95% confidence intervals (CI) from a Poisson model of risk of metachronous bilateral breast cancer using the predictors: age at 1st diagnosis and time since diagnosis*. All cases 1970-1999 included, age 40-79 years.

Category		IRR	95% CI
Age at diagnosis, years	Time since diagnosis, years		
<45	0.25-4	2.0	(1.6-2.6)
	5-9	1.7	(1.3-2.2)
	10-14	1.1	(0.8-1.5)
	15-29	1.0	ref.
45-54	0.25-4	1.2	(1.0-1.5)
	5-9	1.0	(0.8-1.2)
	10-14	1.1	(0.9-1.4)
	15-29	1.0	ref.
55+	0.25-4	1.3	(1.1-1.5)
	5-9	1.3	(1.0-1.5)
	10-19	1.1	(1.0-1.4)
	15-29	1.0	ref.

*Adjusted for calendar period of first diagnosis.

Figure 1.

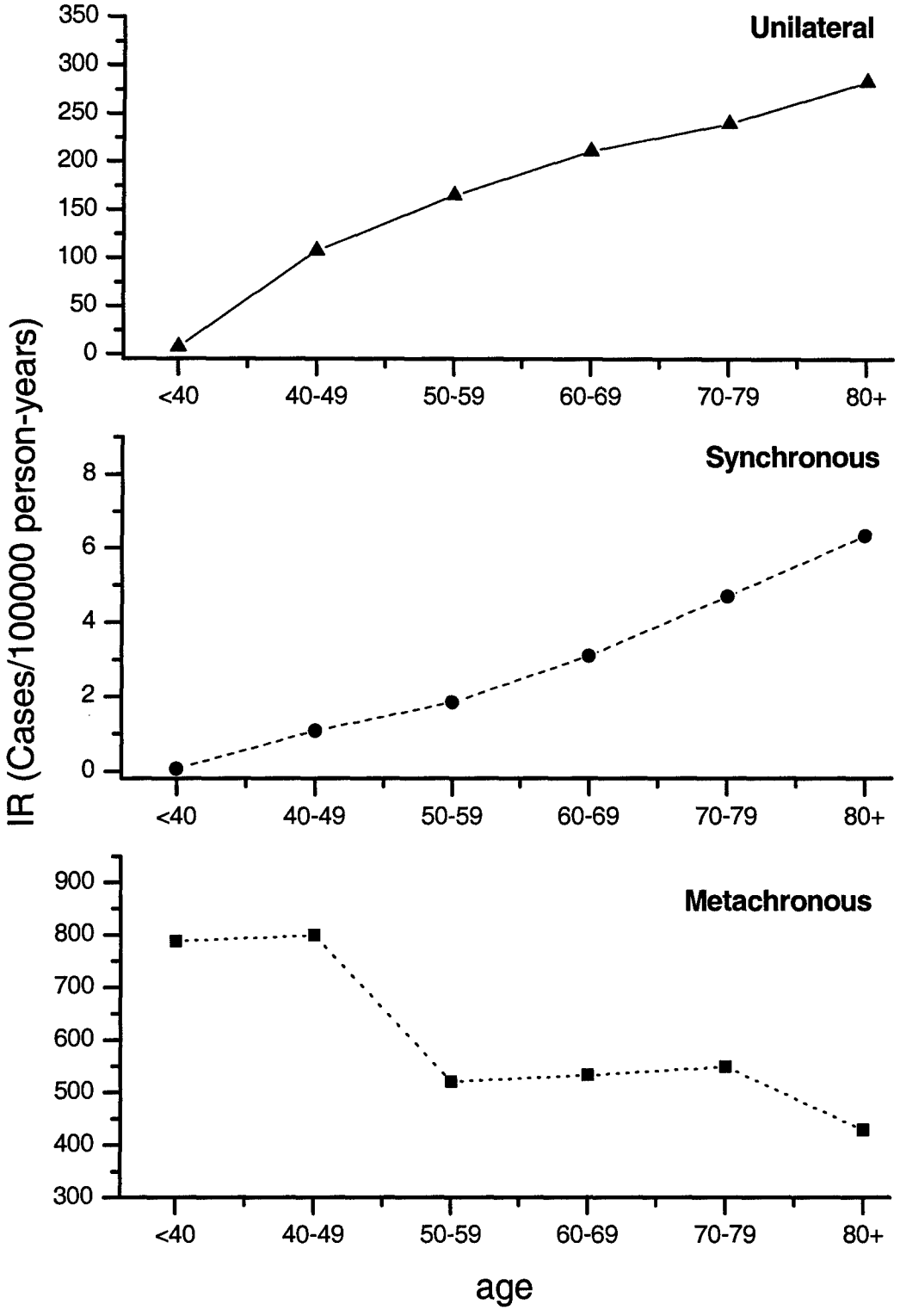

Unilateral
Synchronous
Metachronous
IR (Cases/100000 person-years)
age
<40
40-49
50-59
60-69
70-79
80+
350
300
250
200
150
100
50
0
8
6
4
2
0
900
800
700
600
500
400
300

Figure 2.

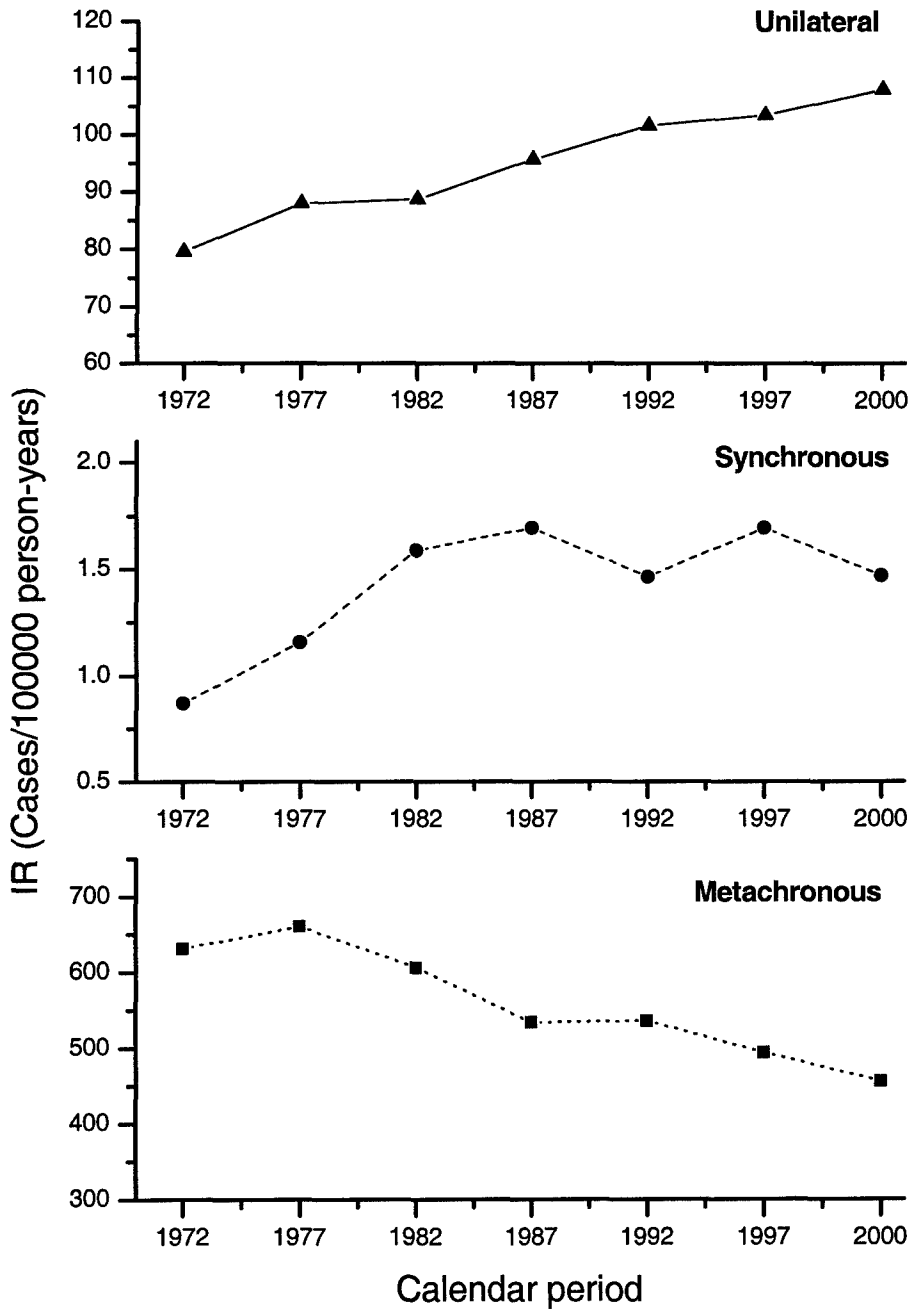

Unilateral
Synchronous
Metachronous
IR (Cases/100000 person-years)
Calendar period
120
110
100
90
80
70
60
2.0
1.5
1.0
0.5
700
600
500
400
300
1972
1977
1982
1987
1992
1997
2000

Figure 3.

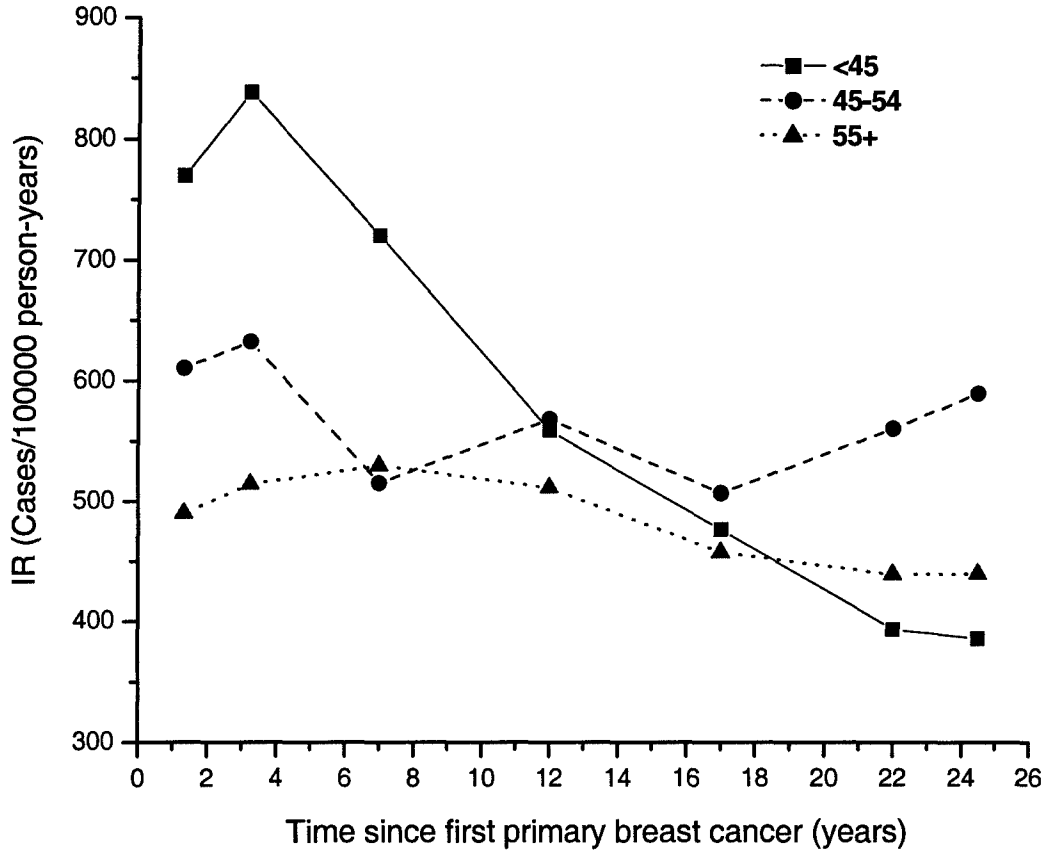
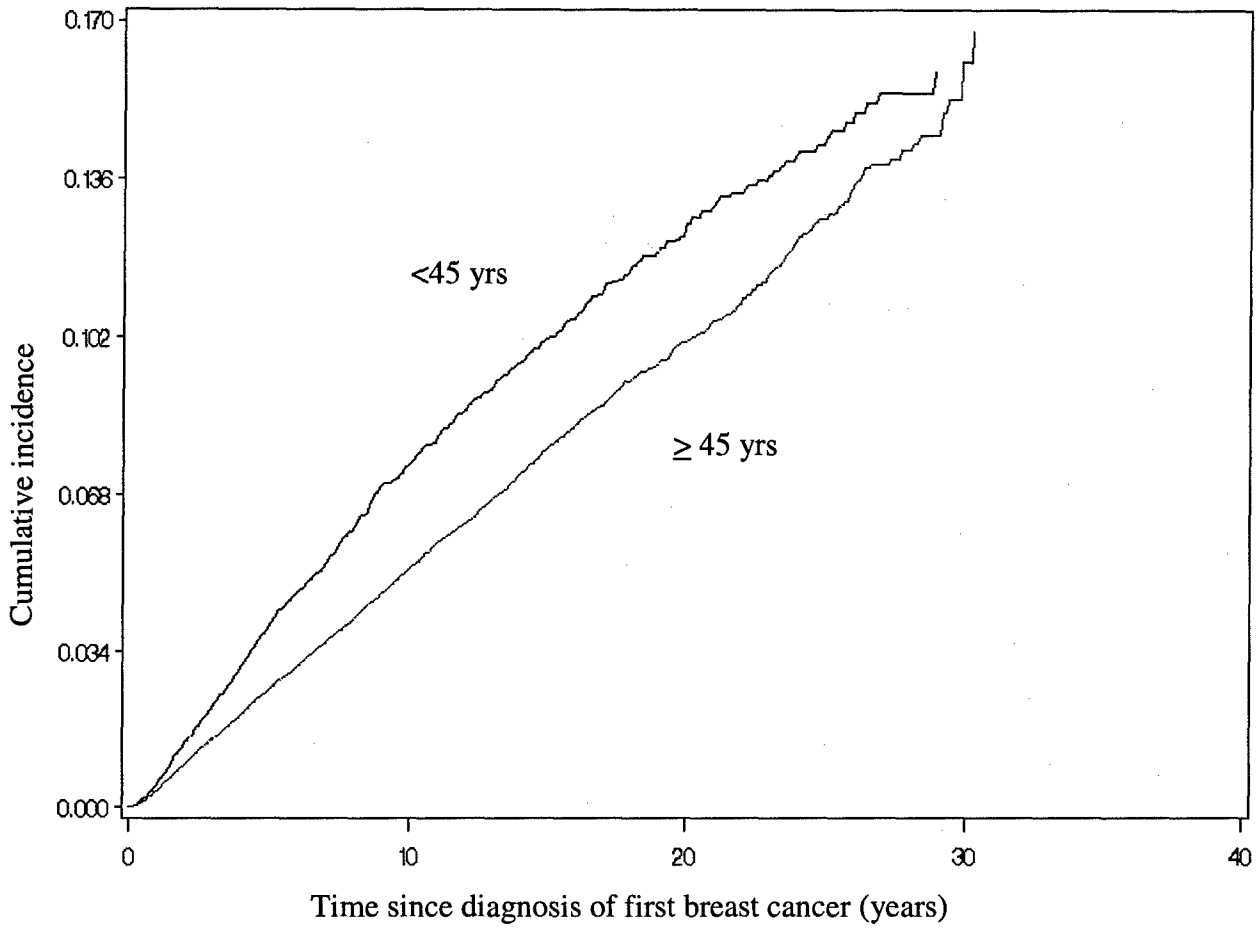

900
800
700
600
500
400
300
IR (Cases/100000 person-years)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
Time since first primary breast cancer (years)
<45
45-54
55+

Figure 4.


0.170
0.136
0.102
0.068
0.034
0.000
Cumulative incidence
<45 yrs
≥ 45 yrs
0
10
20
30
40
Time since diagnosis of first breast cancer (years)

Manuscript in preparation

Occurrence patterns of Inherited Breast Cancer. A Scandinavian Twin and Sibling Study

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Table 1 Number of Twin pairs from Sweden[α], Denmark[β] and Finland[ϕ] with at least one twin sibling affected with breast cancer.

	Twin pairs	Monozygote*	Dizygote*
Sweden	1110	396 (33)	714 (39)
Denmark	770	267 (21)	503 (28)
Finland	260	65 (3)	195 (7)
Total	2140	728 (57)	1412 (74)
Time to diagnosis- yr		8.3	11.1
20-year cumulative incidence		17%	11%
Concordance rate		7.8%	5.2%

* In parenthesis number of concordant breast cancer twin pairs.
[α] Swedish cohort includes breast cancer cases during 1958-1999.
[β] Danish cohort includes breast cancer cases during 1943-1998.
[ϕ] Finnish cohort includes breast cancer cases during 1976-1996

Table 2. Incidence rate of breast cancer in sisters to twin sisters with breast cancer diagnosed in Sweden, Denmark and Finland. 2140 twin pairs with breast cancer included in the analysis. Swedish cohort includes breast cancer cases during 1958-1999. Danish cohort includes breast cancer cases during 1943-1998. Finnish cohort includes breast cancer cases during 1976-1996

	Time since diagnosis of first twin sister's breast cancer									
	0-4 years		5-9 years		10-14 years		15+ years		Total	
Age at 1st twins diagnosis	cases per person-year	%	cases per person-year	%	cases per person-year	%	cases per person-year	%	cases per person-year	%
Monozygotic Twin pairs										
<40	1/179	0.56	1/144	0.69	1/113	0.89	2/235	0.90	5/671	0.74
40-54	9/1062	0.85	8/797	1.00	1/583	0.17	7/1053	0.57	25/3495	0.72
55+	12/1632	0.74	9/1066	0.84	3/611	0.49	3/462	0.65	27/3770	0.72
Total	22/2873	0.77	18/2007	0.90	5/1306	0.38	12/1750	0.68	57/7936	0.72
Dizygotic Twin pairs										
<40	2/383	0.52	0/321	0.00	3/265	1.13	2/524	0.40	7/1494	0.47
40-54	6/1939	0.31	3/1431	0.21	7/1054	0.66	14/1843	0.76	30/6267	0.48
55+	14/2955	0.47	8/2060	0.38	7/1302	0.54	8/1080	0.74	37/7396	0.50
Total	22/5277	0.42	11/3812	0.29	17/2622	0.65	24/3447	0.70	74/15157	0.49

Figure 1. Nelson-Aalen estimates of breast cancer in twin sisters to a breast cancer patient from Twin pairs in Sweden, Finland and Denmark.
(Black- monozygotic, Red – dizygotic)

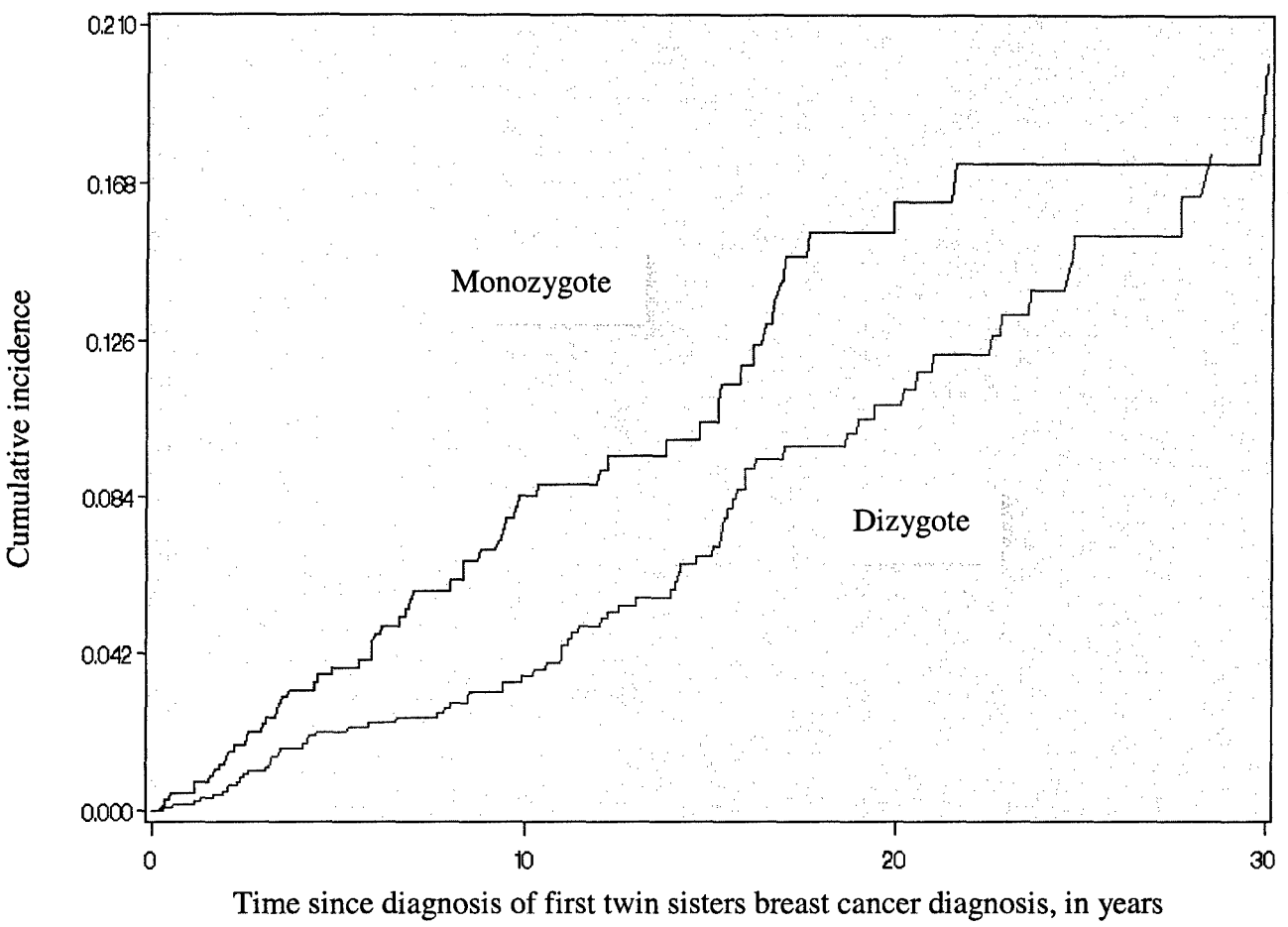

Figure 2. We resorted the largest resource on familial cancer, the Swedish 'Multi-Generation Cancer Database' (described in the Final report: Task 4), and used the Nelson-Aalen cumulative hazard estimate methods to describe the risk in a woman followed from the age at diagnosis in her sister. Our preliminary results show that the risk is relatively constant (straight line in Nelson-Aalen plot). These results are in agreement with the prediction of the model by Peto and Mack.
Black line represents the results when all sisters in the family are included in the analysis. Red line represents the results when the two oldest sisters only are selected in the families with more than two daughters. Results were very similar in both cases.

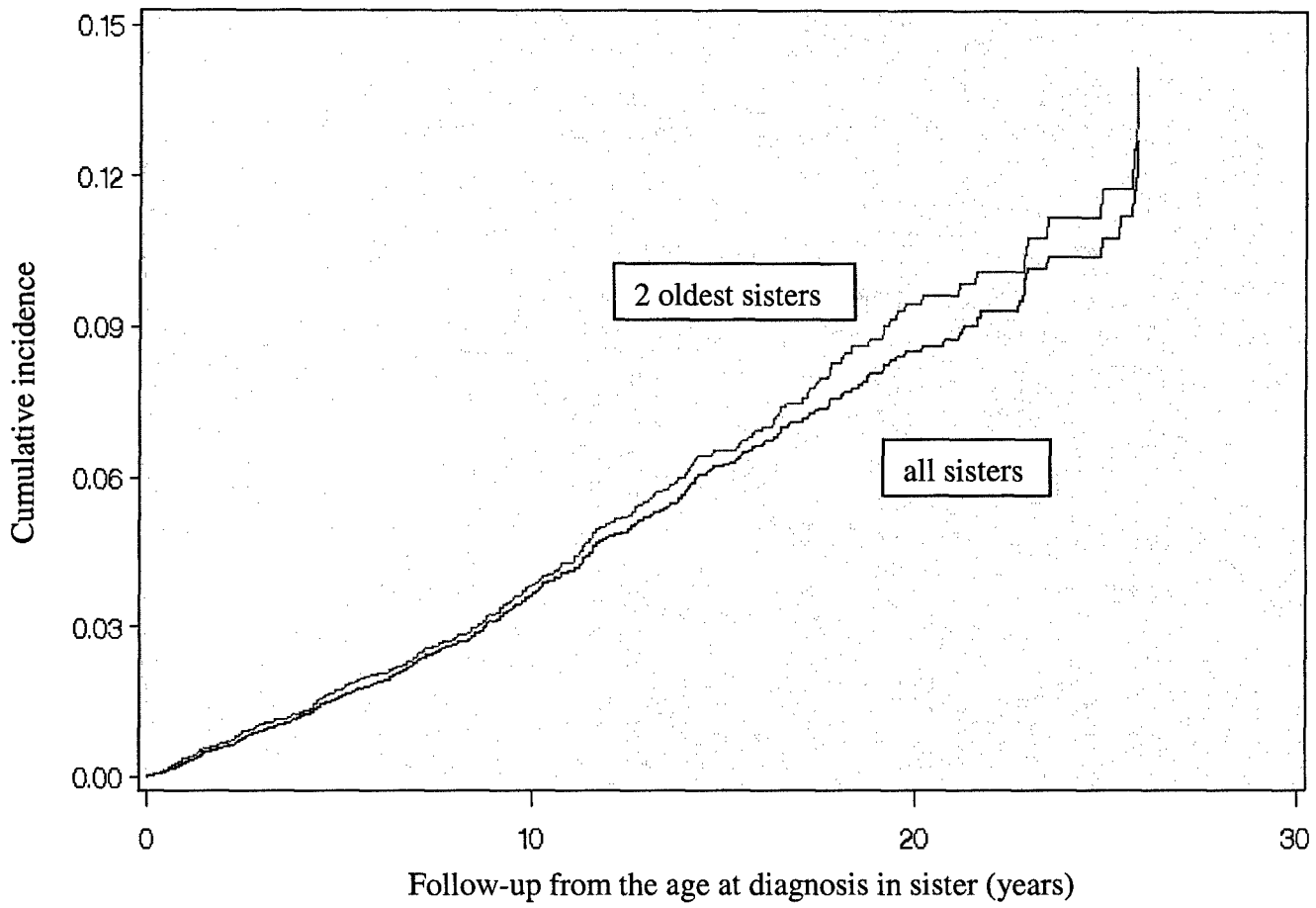

Figure 3. We calculated age-specific annual incidence of invasive breast cancer in the sister to the breast cancer patient (index sister) estimated annually after the age of diagnosis in the index sister (A) or estimated at any time (B). As a comparison, incidence is shown for all women in the Database (0-68 years old) that are representing general Swedish population (C). Our data show that the sister's age-specific incidence rate (only age groups <50 years) is more constant than the incidence of general population when studied after the age when the index sister was diagnosed with breast cancer.

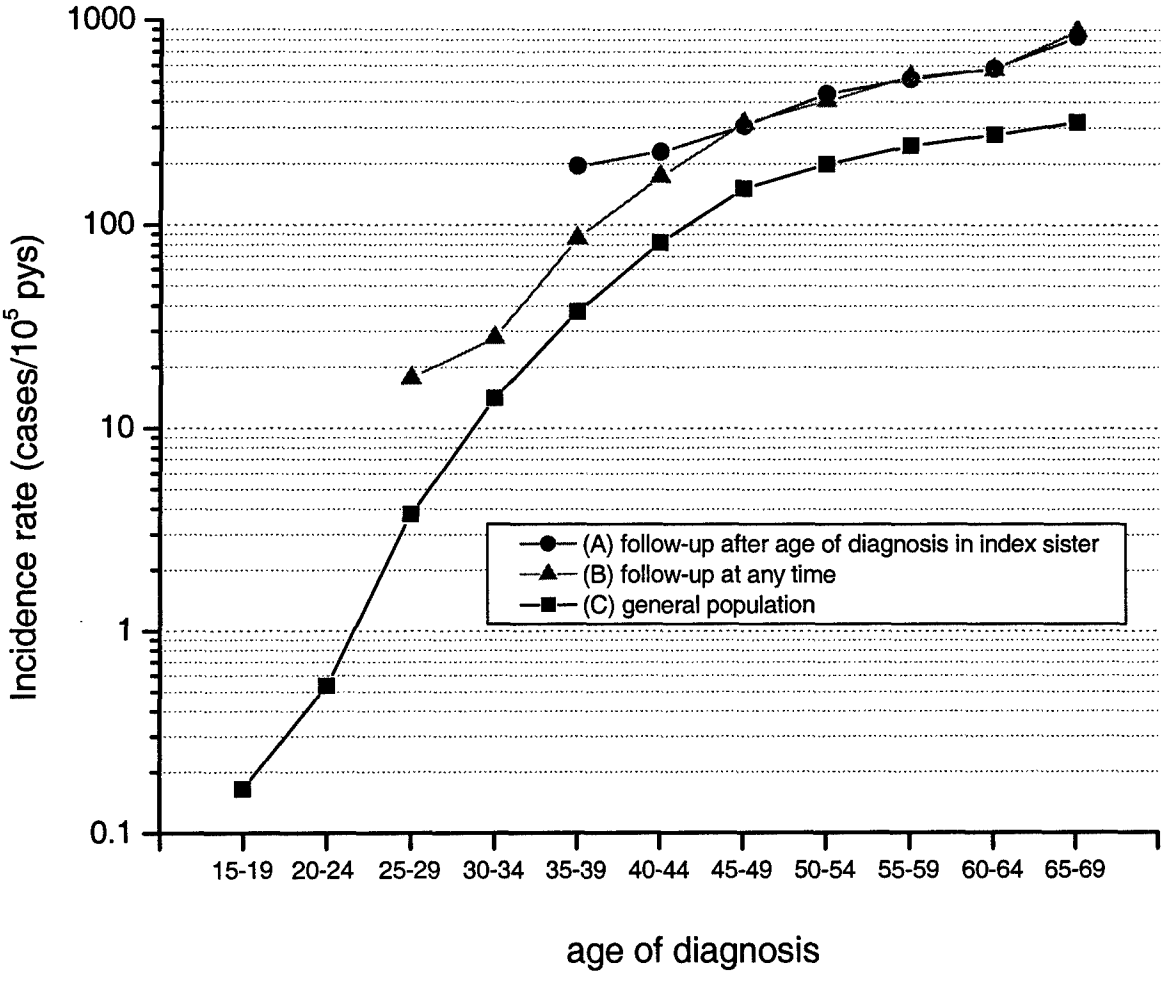

Figure 4. Same as for sisters, the Nelson-Aalen cumulative hazard estimate was presented to describe the risk in a mother followed from the age at diagnosis in her daughter. We had power to follow mothers for more than 50 years after the age of diagnosis in daughter. When the age of daughter was stratified (<45 and >=45 years) we could show that the incidence rate was same for both categories what is in agreement with the model by Peto and Mack predicting constant incidence rate that is independent of the age at diagnosis in index (in this case daughter).

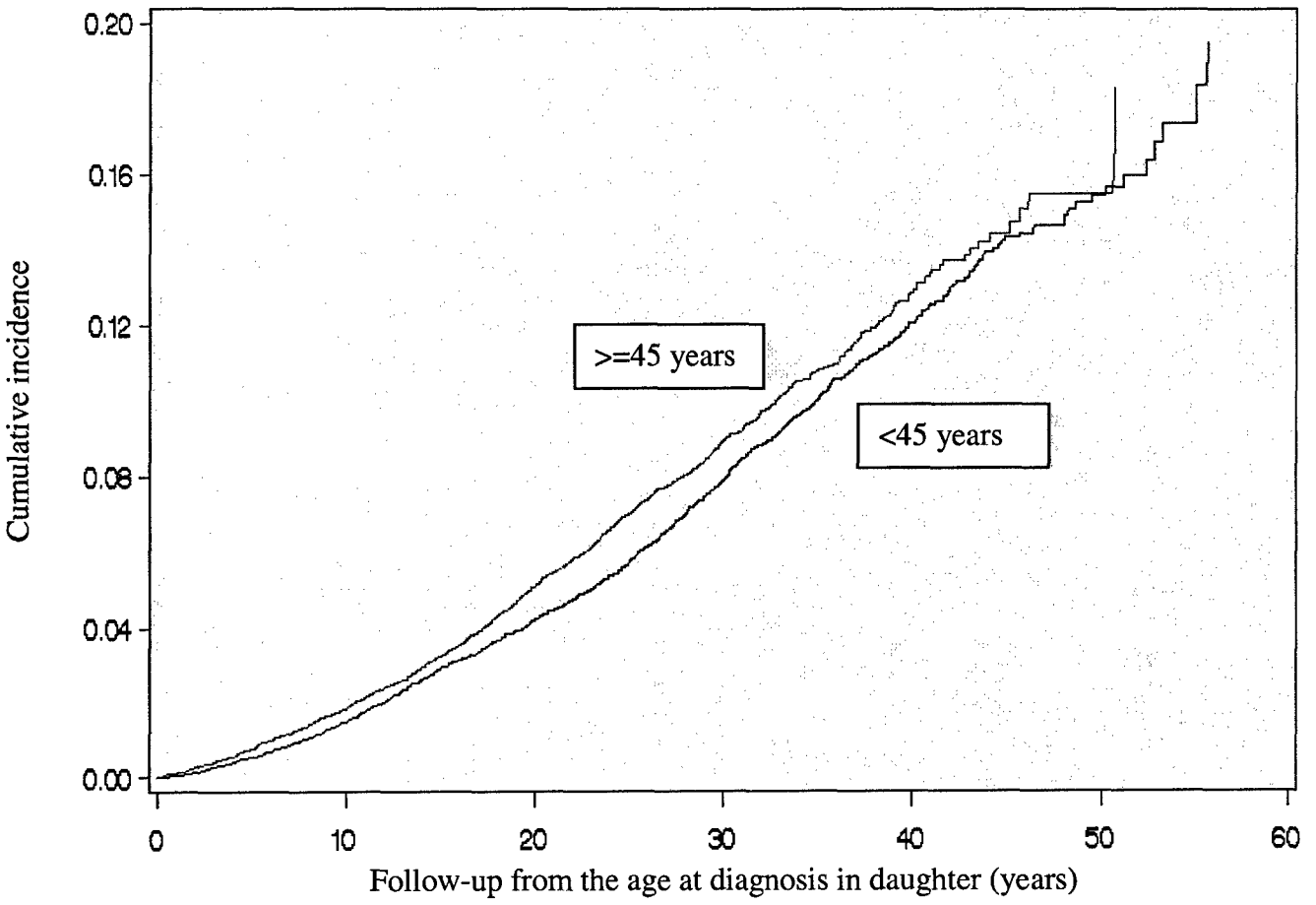

Figure 5. We calculated age-specific annual incidence of invasive breast cancer in the mother of the daughter with breast cancer estimated annually after the age of diagnosis in the daughter (A) or estimated at any time (B). As a comparison, incidence is shown for all women in the Database that are representing general Swedish population (C). Our data show that the mother's age-specific incidence rate (only age groups <60 years) is more constant than the incidence of general population when studied after the age when the daughter was diagnosed with breast cancer.